EXHIBIT C

Appeal No. T892/06-3310

European Patent No. 764 447 B1

(Application No. 96114439.1)

Bayer Corporation

Opposed by

Baxter Healthcare Corporation

Grounds of Appeal submitted by Appellant

Baxter Healthcare Corporation

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3 August 2006

Eric Potter Clarkson LLP
for the appellant

Contents

1. REQUESTS

We maintain the requests in our Notice of Appeal.

We maintain all of our submissions, documents and arguments submitted during the opposition phase.

2. SUMMARY OF APPELLANT'S CASE UNDER ARTICLE 56 EPC

1. It was already well known to use the solvent-detergent (SD) process (steps (a) and (b) of the opposed claim) to reduce viral titre in antibody solutions.

2. It was known to add a low pH incubation step (step (c) of the claim), either to ensure that the anti-complementary activity (ACA) was low or to further reduce viral titre.

3. It was known, in the context of processes for preparing antibody solutions that included an SD step, also to include a subsequent step to reduce ACA.

4. The specific parameters in step (c) of Claim 1, even if these parameters provide bare novelty over the prior art, have not been shown to contribute a surprising technical effect and thus cannot be regarded as indicating that there was an inventive step. In particular it is incumbent upon the patent proprietor to demonstrate this surprising technical effect across the full range of each limitation, and especially in relation to those limitations to which the patent proprietor is pointing when trying to demonstrate a difference between his invention and the prior art.

5. Not all solvent-detergent (SD) treatments will raise ACA sufficiently to cause a problem. To the extent that the claim covers SD processes in which the ACA is not raised to a level that makes the antibody solution unsuitable for i.v. administration, then there is no problem in relation to which the claimed process can represent a solution.

6. The data in the patent do not even establish that the problem has been solved in relation to the patentee's specific process.

3. LACK OF INVENTIVE STEP OVER THE PRIOR ART

3.1 Lack of inventive step over D11

D11 can be taken as the closest item of prior art. The process set out in the left-hand column on page 82 discloses:

(1) an SD step (*"The salt-poor solution ... was then treated with a mixture of 0.3% tri-(n-butyl)phosphate (TNBP) and 1% Tween 80, pH 4.6-4.8, for at least 8h at 25° C for viral inactivation."*),

(2) followed by removal of the residual SD reactants (*"Residual reactants from the viral inactivation step were removed ..."*),

(3) a low pH step (pH4.25) to reduce ACA (*"The paste ... was prepared as a 5% protein solution in 10% maltose, pH4.25 ... several batches could be combined and heated at 50°C for 1h"* plus lines 3-6 on page 85), and

(4) a pH4.25 treatment (*"Each batch was then diafiltered against at least 5 vol of 0.0025 M Na acetate, pH 4.25, ... The solution was formulated in 10% maltose, sterile filtered and filled. To provide an accelerated sterility check, the final containers were held at 25°C for 21 days prior to storage at 2-10° C."*)

Hence, the D11 process discloses steps (a) and (b) of the claim and a subsequent step to reduce the ACA. The patentee's basic position since the application was first filed has been that those in the art did not appreciate that SD would raise ACA to unacceptable levels and that, if they noticed this but saw no aggregates, they would not know how to lower the ACA. In D11, we see (paragraph bridging pages 84 and 85) that the authors knew that ACA was high and needed to be lowered. (Indeed, the patentee's 14 February 2006 response, section 3.6, admits as much.) D11 describes lowering ACA by means of a low pH incubation and does not describe looking for aggregates.

The ACA-lowering incubation in D11 was conducted for only an hour instead of at least 10 days. However, from **D5** page 165 (2nd complete paragraph), it can be seen that it was known that the temperature of a low pH incubation, conducted in order to reduce ACA, affected the duration that was necessary: at a higher temperature, the incubation could be shortened. An optimum temperature was 37°C. The results in the patent were almost all performed at 5°C or 22°C (although Table 7 refers vaguely to 20-27°C) so it appears that the patentee has simply opted to carry out the incubation at a sub-optimal temperature, thus necessitating a longer incubation. There is no inventive step in this. D5 can be taken either as prior art or as "expert opinion", establishing beyond any doubt the rather obvious fact that the reaction will take longer at a lower temperature.

Moreover, as discussed in detail later in section 4.1, the data in the patent do not show that an incubation of 10 days provides any technical effect over, for example, a one day incubation at 37° C. For a majority of data points where ACA results are provided in the patent for a 10 day incubation, it appears that the ACA was acceptable well *before* 10 days.

We acknowledge that we cannot show that the ionic strength in the ACA-lowering step of D11 was below 0.001. However, the patent contains no comparative data to show that the process operates surprisingly more effectively at an ionic strength of less than 0.001, compared to whatever ionic strength would have been the case in the D11 ACA-lowering step.

The legal standard is very clearly set out in the *Case Law of the Boards of Appeal*, section I.D.6.5 (page 121 of the English language edition):

> *"According to the established case law of the boards of appeal, features which do not contribute to the solution of the problem set in the description are not to be considered in assessing the inventive step of a combination of features (citation). According to this decision, in assessing the inventive step of a combination of features, consideration had to be given to the feature only if the applicant had provided evidence that it contributed, either independently or in conjunction with one or more of the other features, to the solution of the problem set in the description (citations). Therefore, only those claimed features are to be considered which contribute causally to the solution of the problem (T285/91). In T294/89 the board stated that the additional feature provided no surprising advantage and did not make any contribution to solving the problem indicated. Hence, the said additional feature was not relevant for assessing the inventive step of the combination of features claimed."*

Hence, no inventive step can be identified in lowering the ionic strength to below 0.001.

Claim 1 of the patent therefore lacks an inventive step over **D11**, taken alone or in conjunction with **D5**.

There is a further, separate, reason for regarding Claim 1 as lacking an inventive step over D11. At the end of the D11 process, the antibody solution is held for 21 days at pH4.25. This is stated to be an "accelerated sterility check" and is not disclosed as being for the purpose of reducing ACA. However, this is immaterial, since the function or technical effect of step (c) is not stated in the claim. Such accelerated sterility checks on the final product were (and are) common in this art, in order to ensure the absence of contamination.

We acknowledge that we cannot show that the ionic strength in this last step of the D11 process was less than 0.001. The ionic strength in the final D11 step can be calculated reasonably precisely, because of the disclosure of the diafiltration of the antibody solution against 0.0025M Na acetate. Since sodium and acetate ions are monovalent, the ionic strength due to the NaAc would therefore be at least 0.0025. (The total ionic strength might be higher, due to the presence of whatever acid was added in order to bring the pH down to pH4.25.) Thereafter, the preparation was simply formulated in 10% maltose, which would not have affected the ionic strength.

The patentee has produced no evidence to show that the level stipulated in the claim provides any surprising advantage compared to the level in D11. As noted above, EPO jurisprudence requires such evidence in order for an inventive step to be recognised. Moreover, **D2** had already taught the desirability of having an ionic strength of below 0.001 in the final container for intravenously administrable antibody solutions:

> *"The pH of this* (ISG) *solution is adjusted, and the ionic strength of the solution is reduced, to a level such that the monomer content of the ISG is greater than about 90% and the actual and latent anticomplement activity is such that the ISG product is rendered intravenously injectable. The pH and ionic strength are maintained at the above levels during protein concentration adjustment, sterilisation, filling into final containers, and the like."* (Column 4, lines 33 to 41, emphasis added)
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> *"Preferably, the ionic strength, as defined, is less than about 0.001."* (Column 6, lines 46 to 47)

Hence, claim 1 lacks an inventive step over D11 taken alone, or together with **D2**.

3.2 Lack of inventive step over D6

Towards the end of the right-hand column on page 6944, **D6** discloses the use of an SD step in order to inactivate virus in a gammaglobulin preparation. The subsequent removal of the SD reagents is not explicitly stated but, as noted above, would inevitably form part of the process.

The disclosure then states:

> *"Finally, to prepare intravenously tolerable immunoglobulin the globulin was held at pH 4.1 for 21 hours at 37°C in the presence of 350 units of pepsin per gram of protein."*

The step in D6 includes pepsin but the presence of pepsin is not excluded by the wording of the opposed claim. The reference to preparing intravenously tolerable immunoglobulin suggests that this step was undertaken to reduce ACA, since it was well known (as is acknowledged in the patent itself at [0002]) that a high ACA meant that the solution was not intravenously tolerable.

The ionic strength is not disclosed and the duration of the low pH incubation is clearly much shorter than that specified in the claim. However, as noted above, there is no evidence in the proceedings to suggest that these differences have a significant, let alone a surprisingly advantageous, technical effect. We note, for example, that the temperature in the D6 step was 37°C. The highest temperature range that was used in the patent was 20-27°C and most of the data were obtained at only 5 or 22°C. The higher the temperature, the faster the reaction will proceed. Hence, a 21 hour incubation at 37°C, as in D6, may well be comparable to a longer incubation at a lower temperature. Indeed, D5, at the bottom of page 165, discloses that 37°C is the optimal temperature for ACA reduction and that a period of around 20 hours is sufficient in order to reduce the ACA satisfactorily. The patentee has presented no evidence to the contrary, so one must conclude that the 10 day limitation in the claim is without technical significance in the context of reducing ACA to an acceptable level.

We therefore submit that the process of the patent makes no contribution to the art, and the claim lacks an inventive step over D6.

3.3 Lack of inventive step over D14

On page 7, **D14** clearly discloses a process for preparing an antibody-containing solution that includes the step of "SD Virus Inactivation", followed by "Removal of TNBP and Triton X-100" and then a step of "pH4 treatment". D14 can therefore be taken as the closest item of prior art, as an alternative to D11.

The product of the D14 process is an IVIG product that has clearly been approved for human use, indicating that it had an acceptable ACA. Hence, the alleged problem that was allegedly solved in the patent, namely preparing an intravenously injectable IVIG product with a low ACA and a low viral titre, had already been solved. **D15** is an internal report (the background to which is explained in paragraphs 5 to 8 of the **D24** Teschner declaration), showing that the commercially-available product of the D14 process had an acceptably low ACA level, namely 47.6 CH_{50}/ml according to the European Pharmacopoeia assay that was used.

The only objectively-determinable problem is therefore to provide a *superior* process. However, there is no evidence in these proceedings that the patentee's process is surprisingly advantageous compared to the process of D14, either in terms of viral titre, ACA level or process efficiencies.

Claim 1 of the opposed patent can therefore immediately and clearly be seen to lack an inventive step over D14.

It is unnecessary to consider the individual parameters of the claim. Nevertheless, for completeness, we shall now do so.

Steps (a) and (b) of the claim are clearly disclosed in D14. D14 also discloses a step of exposing the antibodies to pH4, which is clearly within the pH range specified in step (c) of the claim. In step (c) the temperature range of 2-50°C is so broad as to encompass all of the temperatures that would be likely to be used by a person skilled in the art when handling immunoglobulin solutions. The Board will, of course, appreciate that the range includes typical room temperatures. Hence, unless the prior art specifically stated that a higher or lower temperature was used, this parameter can be assumed to be present.

The "missing" parameters in D14 are the particular ionic strength and the fact that the step should last for at least 10 days. However, given that the D14 product was clinically acceptable, neither of these apparent differences can be considered to have contributed in an inventive way to the solution of a problem.

Moreover, as noted above, **D2** had already disclosed the advantage of using a low ionic strength (indeed, the same specific upper limit of 0.001 that is specified in the claim) in the context of a low pH treatment of immunoglobulins. It was therefore obvious to include this parameter and, even if the Board does not accept that the claim lacks an inventive step over D14 alone, then we submit that it lacks an inventive step over a combination of D14 and D2.

The other parameter is the 10-day duration of the incubation. However, as we show in more detail below, in section 4.1, there are no comparative data to show that a 10-day incubation offers any surprising advantages.

We therefore conclude that the claim lacks an inventive step over D14, either taken alone or together with D2.

3.4 Lack of inventive step over D10

In columns 2 and 3, **D10** discloses a process for preparing IVIG solutions, comprising an SD step (including, of course, removal of the SD reagents) and adjustment of the pH to pH 4 (see column 3 lines 20 to 23) and storage for 22-24 hours at 37° C.

The ionic strength is not stated but is likely to be low by virtue of the diafiltration against water (column 3 lines 51 to 53), following which there does not seem to be any step that would increase the ionic strength. As indicated above, the patentee has not produced any comparative data to show that the upper limit of 0.001 in the claim produces a surprising technical advantage in relation to processes in which the ionic strength is already low and, of course, this particular upper limit had already been disclosed in D2.

Again as noted above, there is nothing in the proceedings to suggest that the minimum duration of 10 days is technically significant.

Hence, the claim lacks an inventive step over D10.

3.5 Lack of inventive step over D23

D23 is principally concerned with the use of low pH conditions to reduce viral titre in the preparation of IVIG solutions. In some instances, pepsin is included and, as can be seen from Figure 3, the viral titre came down to a minimal level after about one week at pH 4.4 in the presence of pepsin. Figure 4 shows that, if pepsin is omitted, then it can take several weeks for the viral titre to come down to the minimal level. Therefore, an incubation lasting several weeks (i.e. more than the minimum duration of 10 days specified in the claim) would be adopted by one skilled in the art who chose to operate the process without pepsin. The presence of pepsin clearly speeds the process up but it also has the disadvantage of degrading the immunoglobulin molecules, producing the "fragment" that is referred to in the very last sentence of the article. This represents a waste of the immunoglobulin material. Hence, the person skilled in art could choose to include pepsin, in order to speed the process up, and would then accept the loss of yield, or could operate the process for longer periods without pepsin, in order to avoid the loss of yield. There is no inventive step in choosing one over the other. Moreover, omitting the pepsin would allow the low pH incubation to serve as an accelerated sterility check, as in D11.

At the end of page 8, *"It is concluded that NaCl has no influence on the inactivation of SFV."*. Hence, there would be no reason for the person skilled in

the art to include NaCl in the incubation and, in the absence of added NaCl, the solution would have a low ionic strength.

We acknowledge, of course, that the purpose of the low pH incubation in D23 was to reduce viral titre. However, the technical effect of this step is not specified in claim and therefore this part of the claim embraces the incubation disclosed in D23.

In the very final sentence of the article, D23 discloses the addition of the solvent-detergent step to their process. The order of the steps is not disclosed. However, since all of the other documents in the proceedings that disclose a combination of the SD step and a low pH incubation always employ them in that order, it would be logical to do so when putting the D23 disclosure into effect. It should also be remembered that D2 taught that the storage of IVIG solutions at a low pH was advantageous. Hence, for this additional reason, it would have been obvious to make the low pH incubation the final step of the D23 process, rather than an upstream step.

3.6 Conclusion regarding D11, D6, D14, D10 and D23

It can be seen that there were at least five disclosures in the prior art of combining the SD step with an ACA-lowering step and/or a low pH incubation (either to reduce ACA or to reduce viral titre) when preparing an immunoglobulin solution for administration to patients, whereas the opposed patent was filed on the premise that no such combined processes existed and that it was inventive to combine the SD step with a subsequent low pH incubation.

In trying to distinguish the claim from the prior art, the patentee has now been forced to rely on a number of specific parameters in step (c) of the claim, none of which has been demonstrated to provide a surprisingly advantageous technical effect compared to the very similar processes that had been disclosed in the prior art. Accordingly, an inventive step cannot be recognised.

3.7 Lack of inventive step over D2 and D1

In view of sections 3.1 to 3.6 above, the following analysis, which concerns the combination of **D2** and **D1** that we made in the original opposition, may be redundant. Nevertheless, we maintain our arguments regarding this combination of documents.

3.7.1 Using a low pH incubation step was obvious

There were at least two reasons why a person skilled in the art would have regarded it as obvious to include a low pH incubation step in a process for preparing intravenously-administrable immunoglobulin solutions (IVIG), namely (i) to ensure that the anti-complement activity (ACA) was acceptably low or (ii) to provide another viral reduction step.

D2 provides an extensive discussion of the problem of ACA in IVIG solutions and solves that problem (although the problem had actually already been solved, as can be seen from page 165 of D5) by incubating the gammaglobulin solution at a low pH. We draw attention to the following passages in D2:

> *"Incubation of gammaglobulin at pH 4.0 at 37°C for various lengths of time has been observed to reduce the anticomplement activity to low levels."* (Column 2, lines 21 to 23, emphasis added)

> *"The pH of this* (ISG) *solution is adjusted, and the ionic strength of the solution is reduced, to a level such that the monomer content of the ISG is greater than about 90% and the actual and latent anticomplement activity is such that the ISG product is rendered intravenously injectable. The pH and ionic strength are maintained at the above levels during protein concentration adjustment, sterilisation, filling into final containers, and the like."* (Column 4, lines 33 to 41, emphasis added)

> *"The material may be kept at room temperature for long periods in the absence of additives with retention of its monomer content and lack of actual and latent anticomplement activity."* (Column 4, lines 53 to 56)

> *"Preferably, the ionic strength, as defined, is less than about 0.001."* (Column 6, lines 46 to 47)

> *"This material had an ionic strength of 0.001 (as determined by calculation) and a pH of 4.2. (...) Several containers were stored at room temperature and after six months, HPLC results indicate the monomer content was still greater than 99%."* (Column 9, lines 12 to 22)

3.7.2 Applying SD to antibody solutions was well known

By the priority date of the patent (September 1995), the basic solvent-detergent (SD) process was well known in the art as being a highly effective means of reducing the titre of lipid-enveloped viruses in products derived from blood. The process is disclosed in D1, which was published in 1985. It can be seen that the D1 process was disclosed as being applicable to all blood-derived products. Antibody-containing solutions are specifically disclosed in column 6 at line 46 (IgG, IgM, IgA) and at lines 59-61 (immune serum globulin) and in column 7 at line 17 (since blood clotting factor II contains immunoglobulins) and at line 26 (IgM).

In D1 itself, there was no *specific* example of applying the SD process to antibody-containing preparations. However, the following documents show that the SD process had actually been applied to antibody-containing preparations by the priority date of the opposed patent:

D3 (see the title)
D6 (see the sentence beginning *"purified gammaglobulin (fraction II) was then treated..."* towards the end of the right-hand column on the first page)
D7 (see the right-hand column on page S39)

D8 (see, in particular, the reference to intravenous immunoglobulin in table 1 on page 304)
D10 (see the whole disclosure)
D11 (see the middle of the left-hand column on page 82)
D13 (see column 5 lines 28 to 30)
D14 (see page 7)
D23 (see the final sentence on page 10).

We consider that it was therefore common general knowledge that the SD process could be, and had been, applied to antibody-containing preparations in order to reduce viral titre. We also refer to a post-published paper from the inventor (Alonso *et al* (2000) *Biologicals* 28, 5-15; which is newly submitted in these proceedings as **D25**), where, in the context of discussing the safety of immunoglobulin products, the authors state that:

> *"We selected treatment with SD due, in part, to its worldwide acceptance as being efficacious*[9-11]*."*

References 9-11 in this paper are all prior art for the patent.

It should be noted that, although claim 1 of the opposed patent contains separate steps (a) and (b), the removal of the solvent (trialkylphosphate) and detergent is an integral part of the SD process since these reagents are toxic and cannot be allowed to be present in the final product. Removal of the reagents is explicitly disclosed in **D1** at column 9 lines 19 to 24; in **D7** in the middle of the right-hand column on page S39; in **D10** at column 2 lines 23 to 26; in **D11** in the middle of the left-hand column on page 82 (*"Residual reactants from the viral inactivation step were removed..."*); and in **D14** on page 7. Removal of the reagents is implicitly present in the other documents that disclosed the use of the SD process. The patentee has never suggested that step (b) contributes an inventive step to the claim and we cannot imagine that that position would change.

We consider that it was obvious from **D1** to apply the SD process, in order to reduce viral titre, whilst keeping the **D2** process as the final step, in order to reduce the ACA (if it had been raised during the SD step) or to maintain the ACA level (if it was already at an acceptable level).

In terms of the parameters in step (c) of the opposed claim, the pH, temperature and ionic strength are all as disclosed in D2. The duration of the incubation is stated in the claim to be at least 10 days. From the passages in D2 that we have quoted above, particularly the passage in column 4 lines 53 to 56, it can be seen that those in the art would inevitably have incubated the IVIG product for at least 10 days, since the conditions of low ionic strength and low pH are disclosed in D2 as being appropriate for the final preparation in the "final container". In other words, the product would be stored in these conditions; clearly such storage will be for at least 10 days in order to allow for distribution to hospitals and storage therein before administration to patients.

The patentee's position is that it was not obvious to use the D2 process as a final step, having started with the SD process of D1, because the person skilled in the art would consider that the D2 process was only suitable for reducing ACA by

virtue of breaking up (and preventing the reformation of) immunoglobulin aggregates, which (according to the patentee) are not caused in the SD process. The patentee takes the position that the person skilled in the art, having found a raised ACA following the SD process but observing that no aggregates were present, would have been baffled concerning why the ACA was raised and would not have known how to reduce ACA back to an acceptable level. Our response to this is as follows.

D2 is not exclusively concerned with the reduction of aggregates. As can be seen from the passages that we quoted above (page 11), the overall teaching in D2 is to reduce ACA and then maintain it at the reduced level. There is no reason to suppose that the person skilled in the art would have considered that the D2 process would be irrelevant merely because there were no aggregates present.

The issue is purely whether the ACA level in the final product is sufficiently low for it to be administered to a patient without adverse consequences. The person skilled in the art would have measured ACA and, if it was unacceptably high, would have used the D2 process in order to reduce it to an acceptable level. If the teaching in the patent is considered to be technically relevant, then step (c) of the claim will necessarily reduce ACA to an acceptable level, and this is what would have happened when the person skilled in the art used the D2 process following the use of the SD process. Whether the person skilled in the art believes that the reduction of ACA has come about by the reduction of the aggregate content is completely irrelevant. The result is what is important, not the underlying mechanism.

For example, in **D11**, the authors assessed ACA by means of an assay for C4a generating activity. See the paragraph bridging pages 84 and 85, with the assay itself being set out at the bottom left of page 82. The authors did not look for aggregates.

See also the left-hand column on page 144 of **D12**:

> *"It is axiomatic, therefore, that an appropriate test for AC activity is included in the quality assurance battery required for release of the different intravenous immunoglobulin preparations. "*

Two assays were then set out in the remainder of the D12 article. Neither of them involved looking for aggregates.

(Note, incidentally, the disclosure, in the paragraph immediately after the one that we quoted above, of rendering IVIG safe for intravenous infusion by stabilisation at pH 4.25.)

Further, see Col 2 lines 54-59 of **D13**, in which ACA is reduced by exposure to a low pH and/or heat. Nothing is said about aggregates.

Finally, in this context, we refer the Board to the second complete sentence on page 166 of **D5**, which states that

> *"Because of these variations in the composition of "standard" γ-globulin it is imperative to test each new lot for AC activity before it is released for clinical studies."* (Original emphasis)

and the following passage in the second complete paragraph on page 169:

> *"It must be reemphasised that each new lot of pH treated γ-globulin must be carefully tested for AC activity. When the latter persists, the lot must be re-incubated at pH 4 or less and 37°C until it is no longer anticomplementary."*

There is no disclosure of looking for aggregates.

The patentee's submissions to the effect that the person skilled in the art would have been baffled by the raised ACA in the absence of aggregates are unsupported (other than by anecdotal evidence concerning the inventor himself, which has to be disregarded as not relating to the objectively-determined person skilled in the art); and, in the light of D5, D11 and D12, the patentee's position can be seen to be spurious in terms of what those skilled in the art would actually have done.

Moreover, if the patentee were correct in stating that the problem was how to reduce ACA when aggregates were not present, then the claim should be limited to such a process. In other words, the 'third antibody solution' at the start of step (c) should be said to have an unacceptable level of ACA but no aggregates (although we do not acknowledge that such a claim would be valid). At present, the claim covers a process in which ACA is raised but aggregates are present. According to the patentee, the person skilled in the art would have had no hesitation in using the D2 process in order to reduce ACA in such a situation.

Furthermore, the patentee's position concerning aggregates assumes that D1 is taken as the "closest item of prior art" and that the problem that has to be solved is then the reduction of ACA, which is assumed to have been raised during the SD process. However, we consider that D2 should more properly be regarded as the closest item of prior art, since it concerns intravenously-injectable immunoglobulin solutions, which is what the opposed claim is specifically concerned with. The "problem" when D2 is taken as the closest item of prior art is therefore to reduce viral titre, since D2 is not concerned with such a process but the person skilled in the art would certainly have needed to do this in order to prepare an acceptable product. As noted above in section 3.7.2, it was obvious to use the SD process in order to reduce viral titre. Since the D2 process is presented as being particularly applicable when used as the final step of the process (see column 4, lines 38 to 41), it would be logical for D2 to be kept as the final step of the process, with the SD step being employed upstream. If the teaching in the opposed patent is to be believed, then this would necessarily result in a product that had an acceptable ACA level.

We therefore conclude that Claim 1 of the opposed patent lacks an inventive step because it was obvious, starting from D2, to add the SD step of D1 as an upstream step in the process.

3.7.3 The OD erred in their assessment of the prior art

In section 5.4 of the appealed decision, the Opposition Division stated that

> *"Despite the fact that an incubation step could be considered as a means to reduce ACA, there would seem to be no incentive in the prior art to select any particular incubation parameters to be applied after SD treatment as long as the actual problem has not been acknowledged."*

First, lowering of ACA of a solvent-detergent-treated antibody solution was the subject of D11 and therefore both the "problem" and the solution (incubating to lower ACA) were described in the prior art.

Second, as we demonstrate below in section 5, one very good reason why the "actual problem" might not always have been acknowledged in the prior art is that it did not always exist; in other words, the SD process frequently does *not* raise ACA.

Thirdly, the OD seemed to ignore documents such as D5, D11 and D12, which show that those in the art definitely did test IVIG solutions for ACA and the OD ignored documents such as D5, D11, D6 and D2 which taught the person skilled in the art how to reduce an excessive ACA and to maintain it at a lower level. Hence, there is no need to identify a *statement* in the prior art to the effect that the SD step raises ACA to see that the claim lacks an inventive step. Either, in the context of a given process, it does not raise it, in which case there was no problem to solve (as we explain in more detail in section 5 below), or, if it does raise it, then this would be noticed by the person skilled in the art and he would deal with it. In other words, merely identifying the "problem", as set out in the patent, does not indicate an inventive step. The Opposition Division was wrong to reach a contrary conclusion on this point.

3.8 The sub-claims do not add anything inventive

Until such time as the patentee presents auxiliary claim requests, it is unnecessary to consider the validity of the sub-claims. However, in the meantime, we refer to section 2.2 of our original opposition. We also refer to section 2.3 of our letter dated 27 January 2006. As was pointed out in the remainder of that letter and in the **D18** declaration from Dr Crowe, the patent fails to disclose a specific ACA assay protocol. Therefore, the specific ACA values recited in claims 2 to 6 are meaningless.

4. THE DATA IN THE PATENT ARE INADEQUATE TO SUPPORT AN INVENTIVE STEP

4.1 The patent does not show that an incubation of "at least ten days" provides a particular benefit

Although the patentee argues that an incubation of at least 10 days was selected based on experimental conditions, the data do not show that a 10 day time period is necessary or in any way technically significant. The patentee essentially argues that the data in Tables 6 and 7 provided for the selection of the "greater than 10 day" limitation in claim 1 (Bayer February 14, 2006 submission, page 6, second full paragraph).

The patentee does not present data showing ACA measurements for incubations of less than ten days (except for one 9 day incubation at 5°C in Table 5). Without such data, the patentee cannot argue that an incubation of at least ten days is required to reduce ACA to acceptable levels. Indeed, the data in Table 7 of the patent suggest that for many samples the reduction of ACA had reached a plateau before the 10 day time point

Notably, the data presented in Tables 6 and 7 suggest that in most cases, an incubation of 10 days is longer than is necessary to lower ACA to a basal level. For example, samples A1, A2, A3, B2 and B3 had an acceptable ACA without *any* incubation. Further, sample B1 had an "unacceptable" ACA level initially, but had an ACA of "48" after 10 days (well below the acceptable level of 60 defined in the patent, suggesting that an acceptable level was reached before 10 days). Review of the ACA of all of these samples (A1, A2, A3, B1, B2 and B3) as measured after a 10 or 21-day incubation reveals that there was little or no difference (and sometimes an increase) in ACA between 10 and 21 days. This suggests that if an incubation is effective to lower ACA, generally the effectiveness of the incubation in reducing ACA has been reached a basal level *before* 10 days. For example, a one or two day incubation may have been sufficient to reduce the ACA to a basal level, consistent, for example, with the disclosure of D5.

On the other hand, for at least two samples, a 10 day incubation was *not* sufficient to generate a sample with an acceptable ACA value (as defined by the patent). This can be seen in Table 6, which shows that, even after 25 days at 22°C, the ACA was 56 CH_{50} units/ml, and in Table 5, in which, after as long as 21 days at 5°C, the ACA level was still 71 CH_{50} units/ml. Both of these incubations were conducted within the time and temperature parameters of Claim 1, and yet the resulting ACA is still at a level that is indicated in the patent ([0023]) to be above acceptable levels. Hence, the problem (if there was one) had not been solved.

The data in Table 7 can be summarised as follows:

Sample	Result
A1	ACA already acceptable without incubation
A2	ACA already acceptable without incubation; probably reached basal ACA level in less than 10 days
A3	ACA already acceptable without incubation; probably reached basal ACA level in less than 10 days
A4	10 days insufficient to reduce ACA to acceptable level
B1	ACA reduced to acceptable level after 10 days; probably reached basal ACA level in less than 10 days
B2	ACA already acceptable without incubation; probably reached basal ACA level in less than 10 days
B3	ACA already acceptable without incubation

Hence, only B1 is a sample supporting the claimed invention in that B1 had an "unacceptable" ACA level after SD treatment and reached an acceptable ACA level after a 10 day incubation. But even in this case, there is a question whether a shorter incubation would have been equally effective in view of the fact that further incubation after 10 days did not result in a further significant decrease in ACA.

In sum, the data suggest that on most occasions an incubation that was shorter than ten days would have generated an acceptable level of ACA and, conversely, that sometimes (sample A4) ten days was not long enough. This is hardly a basis to show that "greater than 10 days" is a technically significant parameter that provides an inventive step in the claim.

4.2 The patent shows no effect of ionic strength

The patent describes a number of experiments analyzing the effect of various incubation conditions on ACA. However, all experiments were apparently carried out using the same ionic strength. Thus, no experiment presented in the patent demonstrates any significant technical effect on ACA reduction during incubation compared to a significantly higher ionic strength incubation. There is no basis to assume that the incubations of the patentee resulted in any different ACA reduction than that observed by Barandun (D5) or that a lower ionic strength would be expected to affect ACA reduction. Thus, the patentee has not established that any particular ionic strength has any technical effect.

4.3 The patent shows the same effect of incubation temperature as was known from the prior art

The patent describes incubations at three temperatures: 5°C (Tables 3 & 5), 22°C (Tables 3, 5 and 6), and 20-27°C (Table 7). The effect of different temperatures on ACA reduction is directly compared only in Table 5, which shows that the same sample (apparently divided in half) had an ACA value of 49 when incubated at 22°C, but had an ACA of 71 when incubated at 5°C. (It should be noted that neither '49' nor '71' is an acceptable ACA value, according to the patent. Thus, the incubations in the Examples are not solving the "problem" allegedly identified.)

The patentee commented at page 7 lines 24-25 of the patent that "the reduction in ACA is dependent on temperature". However, these results are simply consistent with those of Barandun (**D5**), who found that temperatures below 37°C were only "partially effective" (D5, page 165, second full paragraph). Indeed, it is not surprising, given knowledge of molecular kinetics and the standard laboratory practice of refrigerating biological samples to prevent degradation, that the patentee observed only a small reduction of ACA when incubating at 5°C, but observed a faster and more significant reduction at higher temperatures. Hence, the patentee has discovered nothing new here.

As noted above, the temperature range specified in step (c) of claim 1 is so broad as to be technically meaningless and incapable of distinguishing the claim from the prior art. In any case, it can be seen that the patentee's much vaunted "data points" add nothing to the prior art understanding of the effect of exposing immunoglobulins to a low pH incubation.

4.4 The data in the patent only involve one pH value (4.25)

The patent provides no data to show that the full pH range claimed (3.5 to 5) works to reduce ACA. All of the experiments in the patent involve the same pH (4.25). Thus, if in fact the patentee continues to argue that they have identified a "new" incubation condition deserving a patent, their claims should be limited to their data, i.e. pH 4.25.

4.5 Very few experiments in the patent show that there is an increase in ACA following SD treatment

As we show in a separate section of these grounds of appeal (section 5), we believe that there are many instances (maybe the majority) of SD processes that do not actually raise the ACA level of the antibody solution. Hence, the basic premise on which the patent is based can be seen to be flawed. It is possible, in principle, that the *particular* SD process described in the patent increases the ACA level but, when one studies the data in the patent properly, it can be seen that many of the data in the patent do not support a conclusion of an unacceptable increase in ACA following solvent/detergent (SD) treatment. Moreover, as we discussed in more detail in section 4.1 above, in most of the cases where an allegedly unacceptable level occurs after solvent-detergent treatment, an

incubation of at least 10 days is not sufficient to reduce the ACA to an acceptable level as defined by the patent. Sample B1 in Table 7 is the *only* data point where SD allegedly raises ACA to an unacceptable level *and* a 10-day incubation results in an acceptable ACA.

The patentee's statement that the patent shows "multiple data points ... that show ACA increase" (Bayer February 14, 2006 submission, page 2, first full paragraph) is not true. Regrettably, in section 5.1 of the appealed decision, the opposition division took the view that "since the burden of proof in this case is on the opponent and the patentee's experimental findings are based on a higher number of experiments it seems clear that the date (*sic*, data) in the opposed patent are not disproved beyond reasonable doubt". We disagree and we submit that the data in patent *itself* are inadequate to support the patentee's position.

We make two points. First, the data presented in Table 7 of the patent show that TNBP-cholate treatment at pH 5.8 more often than not did *not* raise ACA to an unacceptable level. Second, the patent data in general are insufficient to lead one to believe that solvent-detergent treatment necessarily results in an increase in ACA at all.

The ACA values presented in Table 7 (one of the few tables presenting replications of experiments) actually suggest that SD treatment does not necessarily raise ACA levels above "acceptable levels" as defined by the patent. In paragraph 23 of the patent, an "acceptable level" of ACA for a 5% protein solution is said to be "less than about 45 CH_{50} units/ml" and for a 10% protein solution it is said to be "less than about 60 CH_{50} units/ml." Following SD treatment, three (A1, A2, and A3) out of four of the 5% protein solutions in Table 7 had ACA levels below 45 CH_{50} units/ml, i.e. at an acceptable level as defined by the patent, *before* any incubation was performed! Indeed, it is not even clear that the ACA values presented for samples A1, A2, and A3 in Table 7 are statistically different from the ACA values of 22 and 25 presented for the controls in Table 1, i.e. that they were higher than controls not treated with SD (ACA = 22 or 25). In addition, following SD treatment, two (B2 and B3) out of three of the 10% protein samples had ACA levels below 60 CH_{50} units/ml, i.e. at an acceptable level as defined by the patent *before* any incubation was performed. Thus, of the seven data points provided in Table 7, only two samples had an ACA level that was "unacceptable."

To better illustrate how Table 7 shows that the SD treatment did not generally raise ACA to an unacceptable level, we have re-produced below columns 1 and 2 of Table 7 of the patent. Bolded values indicate those ACA measurements that were acceptable, as defined by the patent, following SD treatment but *without* any incubation. As can be readily seen, five of the seven data points in Table 7 represent SD treatments that did not raise the ACA above an unacceptable values.

Sample	Sterile bulk (day zero) (CH_{50}/mL)
A1 (5% IGIV)	**43**
A2 (5 % IGIV)	**31**
A3 (5% IGIV)	**44**
A4 (5% IGIV)	122
B1 (10% IGIV)	> 100
B2 (10% IGIV)	**49**
B3 (10% IGIV)	**53**

Thus, most of the data presented in Table 7 show that SD does *not* raise ACA above acceptable levels.

Moreover, it is not clear that the ACA values presented for the SD treated samples in Table 7 are statistically different from the controls in Table 1 and therefore show any increase at all. For example, in Table 7, four 5% protein samples all treated with the same SD conditions had ACA values of 31, 43, 44, and 122, respectively. Sample A4 (ACA = 122) has an ACA value nearly *four times* that of sample A1 (ACA = 31). This is a surprising amount of variation! In Table 7, the 10% protein samples treated with the same SD conditions also showed a surprising amount of variation (ACA values of 49, 53, and ">100"). In view of the four-fold variation observed for the SD-treated samples, it does not appear that there is *any* statistical difference between initial ACA values for samples A1, A2, or A3 and the ACA of 25 observed for the 'no SD' control in Table 1.

The patentee appears to rely on outlier data (i.e. statistically remote data) to support its point rather than properly analyzing all of the data. Indeed, to the extent that the patentee analyzes their data in sum, they appear to *average* the data, thereby overweighting their outlier data. For example, if the outlier value of "122" in Table 7 is ignored, then the average ACA level falls from 60 (which was the value used in the Figure of the patent) to 39, which is an acceptable ACA level. The patentee's data have such variation that it is not clear how they can compare data between experiments, particularly between their few "no SD" control data points and their later SD-treated data.

Contrary to the patentee's assertions, only Table 1 of the patent provides a comparison of ACA with *and* without SD treatment. Specifically, Table 1

provides ACA values for two SD controls (25 and 22 CH_{50}/ml)[1] as well as one data point each for a TNBP/Tween-80-treated sample (68 CH_{50}/ml) and a TNBP/cholate-treated sample (>100 CH_{50}/ml). (Incidentally, the significance of a level of ">100" units is not explained in the patent. Does this indicate a failure of the assay, rather than a true value?) The patentee assumes that all samples not treated with SD have an ACA of approximately 22-25 and therefore that other ACA values provided in the patent can be directly compared with those in Table 1. However, strictly speaking, the data in the other tables of the patent do not show an increase in ACA resulting from an SD step, because the other tables do not provide a data point for a control sample that did not receive an SD treatment. Indeed, this is necessary as ACA assays involve multiple biological reagents, including cells and biologically active proteins, thereby rendering the assay highly variable when, for example, it is performed on different days. Thus, the patentee's statement that the patent shows "multiple data points ... that show ACA increase" (Bayer February 14, 2006 submission, page 2, first full paragraph) is not true.

In short, the patentee is hardly correct when he states that his data show that SD treatment significantly raises ACA. The statistics simply do not support such a position.

4.6 It is not clear that the experiments in Table 1 of the patent reflect conditions that resulted in a 4log_{10} reduction in virus

The patentee has argued in the opposition phase that the claims require a 4log_{10} virus reduction and has used this as a basis to criticize various references cited by the opponent such as D4 (Bayer February 14, 2006 submission, page 2, first full paragraph) and D13 (Bayer February 14, 2006 submission, pages 2-3, spanning paragraph). However, it is not clear from the patent that the SD conditions used to generate data in the earlier parts of the example in the patent actually resulted in a 4log_{10} reduction. Importantly, the earlier data in the example provide the only measurement of ACA in control "no SD" samples.

The relevant paragraphs of the patent are paragraphs 17, 25 and 31 as follows:

> **[0017]** Next, the TNBP/detergent is added to the protein solution (preferably less than 8% [w/w], pH 5.8) mixed thoroughly, and then incubated above ambient temperatures, for example 30° C, with continuous agitation or mixing. Target TNBP/cholate levels for optimal viral inactivation during the incubation step should be > 3 mg/mL TNBP and > 2 mg/mL cholate as defined by Edwards et al. (8) Moreover, for effective viral inactivation, it is important that the solution is essentially free of particulates in order to facilitate thorough mixing of solvent/detergent and IgG solution. After incubation with TNBP/cholate under these conditions, greater than 5.2 log_{10} reduction of HIV-1 and greater than 4.0 log_{10} reduction of BVDV were detected.

[1] Note that Table 2 includes an ACA measurement of 12 CH_{50}/mL, but does not include a comparison with an SD-treated sample.

[0025] In the control experiment, incubation (-)/SD (-), the SM was not subjected to any incubation or solvent/detergent treatment. In the incubation (+)/SD (-) experiment, the pH of the SM was adjusted to 7.0, the solution was incubated at 30° C for ten hours, and then the pH was reduced to 4.0. In the incubation (+)/ SD, TNBP & Tween 80 (+) experiment, the pH of the SM was adjusted to 7.0, 3 mg/mL TNBP and 2 mg/mL Tween 80 were added to the solution, the solution was incubated at 30° C for ten hours, and then the pH was reduced to 4.0. In the incubation (+)/SD, TNBP & cholate (+) experiment, the pH of the SM was adjusted to 7.0, 3 mg/mL TNBP and 2 mg/mL cholate were added to the solution, the solution was incubated at 30° C for ten hours, and then the pH was reduced to 4.0. The solutions in each experiment were then diafiltered with four volumes CWFI (cold water for injection) and concentrated by ultrafiltration. After addition of dry maltose to 10% w/v, the 5% IGIV solution (pH 4.25) was filtered through a 0.2 µm filter.

[0031] ACA levels were evaluated after incubation with TNBP/cholate at pH 5.8 because better viricidal activity was observed at pH values less than 6.0. Generally, the non-incubated sterile bulk samples of material incubated at pH 5.8 had lower ACA levels than the pH 7.0 samples, but the trend of lowering ACA upon incubation was repeated in the pH 5.8 samples. In fact, the ACA levels continue to decrease beyond the 21 day incubation in samples that initially had elevated ACA levels after incubation with TNBP/cholate at pH 5.8 (Table 6). As was previously noted for the samples incubated at pH 7.0, the lowering of ACA was not due to decreasing levels of aggregated IgG molecules because the material treated at pH 5.8 was essentially monomeric IgG prior to 22° C incubation (HPLC analysis, sample A4, Table 8).

Paragraph 17 is part of the general disclosure of the preferred process of the patent, whereas paragraphs 25 and 31 relate to the specific experiments.

Paragraph 17 states that a 5.2$\log_{10}$ reduction was observed for HIV-1 and a "greater than 4.0$\log_{10}$ reduction" was observed for BVDV. Although it is not completely clear, it appears that these measurements are based on the "preferred" SD conditions involving a pH of 5.8. However, for no good reason that we can discern, the pH of the SD step reported in paragraph 25 was pH 7.0. Paragraph 31 of the patent states that pH 5.8 SD conditions yielded *better* virucidal activity than pH 7 conditions. If the "greater than 4$\log_{10}$ reduction of BVDV" was observed for the pH 5.8 conditions and pH 5.8 conditions are more effective than pH 7 conditions, then the pH 7 conditions may very well not have resulted in a 4$\log_{10}$ reduction of BVDV and thus would not fall within the patentee's claims.

The reduction in viral titre in the specific experiments reported on pages 5 to 7 of the patent does not seem to have been measured, or at least is not reported in the patent. Therefore, the experiment does not necessarily represent an example of the invention. It would be completely inappropriate for the patentee to rely on a process that falls outside of the claims in order to support his claim, particularly when he has suggested that the extent of the reduction of viral titre in step (a) of the claim is an essential and technically significant feature of the claim.

Significantly, the pH 7 conditions were the conditions used to generate the data in Table 1, i.e., the only Table showing a direct comparison of "with" and "without" SD. Moreover, if pH 7 SD conditions did not result in a 4$\log_{10}$ reduction, this suggests either that the patentee's data are not directly relevant for their claims or that their strident arguments that a 4$\log_{10}$ reduction must be explicitly shown in prior art references are not relevant to the ACA raising effect that they purport to observe.

4.7 It cannot be concluded from Table 2 that the increased ACA observed was not due to residual SD

Table 2 is presented in the patent to allegedly show that the increased ACA results that the patentee observed after SD treatment were not spurious increases caused by residual SD in the samples. To this end, the patentee spiked an IGIV sample

with 100 µg/ml TNBP and 100 µg/ml Na cholate and reported that the ACA was 12 CH_{50}/mL, i.e. essentially identical to their control lacking SD.

This experiment is strange as there is no explanation of why a concentration of 100 µg/ml is used to spike the samples. A more logical approach would be to measure the residual amounts of SD remaining after the removal step and, based on those *empirical* data, perform a spiking experiment. Without this being done, it is possible that the patentee's actual SD-treated samples contained higher residual amounts of SD than their spiking experiment assumed and thus had sufficient SD to affect the ACA readings.

In addition, no "control" spiking experiment was performed with Tween, thereby suggesting that the ACA result from the single Tween-treated sample in the patent was due to remaining Tween in the sample.

4.8 Conclusions

- The features of the claim that, in some instances, can be said to provide novelty over the prior art disclosures of a process employing an SD step and a low pH incubation step, namely an ionic strength of less than 0.001 and an incubation time of at least 10 days, have not been shown to contribute a technical effect beyond the ionic strengths and incubation times that had been disclosed in the prior art.

- The data do not unambiguously show that even the patentee's own SD step raises ACA to an unacceptable level. If the ACA level is not raised to an unacceptable level by the SD step, then, at least in terms of the disclosure in the patent, step (c) of the claim appears to be purposeless.

- The data in the patent have not been demonstrated to be examples of the claimed subject matter, since it seems entirely likely that the viral titre in the SD step was not reduced to the extent specified in the claim. Unless the patentee can show that the requisite degree of viral titre was actually achieved, then all of the data in the patent should be disregarded.

- The patent presents only a single Tween experiment, which only describes removal of the detergent with diafiltration (of questionable efficacy), and yet purports to claim *all* SD processes.

5. THE CLAIM COVERS A NON-SOLUTION TO A NON-PROBLEM

5.1 An SD step does not necessarily raise ACA to an unacceptable level

Based initially on the **D4** reference, it has been an important part of our opposition that the entire basis of the patent is flawed. The patent is based on the assertion that the SD process necessarily raises the ACA level of an antibody solution to an unacceptable level and that therefore a further step is necessary in order to bring the ACA level down. As we have shown in section 4 above, one cannot even

conclude that the ACA level is raised to an unacceptable level in the context of the particular SD process that was used by the patentee. As we have shown in prior art documents (D3, D8, D13 and D26), as well as with experimental data (D4), there are SD processes that do not raise the ACA level to an unacceptable extent and in relation to which there is therefore no problem that needs to be solved. If there is no problem to be solved, then there cannot be a solution to that problem, whether inventive or non-inventive.

At the very least, if the patentee is going to continue to assert that the SD step can cause this problem, then Claim 1 should be limited to processes in which this happens. In other words, Claim 1 should be amended to include in step (a) a limitation that the step raises ACA to an unacceptable level. (In stating this, we are not implying that the thus-amended claim would comply with the EPC, particularly not with Article 84 thereof.)

The experiment reported in D4 compared two antibody-containing preparations, one of which had been exposed to an SD step and the other of which had not. The ACA titre at the end of the process was exactly the same in each case. (The patentee has suggested that the fact that the ACA levels were precisely the same, namely 45.6, is somehow suspicious. However, the underlying data can be presented to the Board on request and have been presented to the patentee in the context of other proceedings involving this family of patents.)

D3 provides further evidence that the SD step does not necessarily raise the ACA level. In D3, a comparison was made between Venoglobulin-I and Venoglobulin-S, the latter having been subjected to the SD process of D1. Both of these are "native" IGIV preparations, as opposed to the heat-aggregated preparations that were also made. See Figs 1 to 3. The low complement binding of the SD-treated product shows that the SD treatment does *not* raise ACA.

D13 (which was published before the priority date) is another example. Referring to column 5, lines 28 to 30, one half of a batch of the IVIG solution was subjected to a solvent-detergent process and the other half was not subjected to this process. It can be seen from Table 5 in that column that there was no significant difference in the ACA level between the two preparations.

See also **D8** (Pehta, 1996), which is a post-published document that we are citing as *expert evidence* of the fact that the SD process does not necessarily raise ACA. The passage bridging pages 307 and 308 discloses the SD treatment of IVIG (intravenous immunoglobulin) preparations and compares the product with non-SD-treated IVIG. See page 308, first complete sentence:

> *"The results of this study show no evidence of serious adverse events with any of the products infused and no statistical difference in the rate of mild reactions after infusion."*

If the SD process had raised the ACA of IVIG to clinically unacceptable levels, which is the supposed problem addressed in the patent, there would certainly have been a difference in the SD-treated and non-SD-treated products.

Finally, we are submitting a new document (**D26**) as still further evidence that the SD process does not materially raise ACA. See Table 5, the right hand column of which relates to the product of a process that is described in the last paragraph of that page. The process involves first and second SD steps. Table 5 gives the results of various analyses of the product before and after that SD step. The ACA level is measured in units of mg/CH'50 (whereas the units used in the patent are CH_{50}/ml), such that, the higher the number, the lower the ACA. It can be seen that the ACA rises slightly from 1.17 units to 1.07 units. This equates to about a rise from about 42 CH_{50}/ml to about 46 CH_{50}/ml. The rise is essentially immaterial, and both values are likely to be acceptable in an intravenously administrable product.

Hence, the claimed process is not inventive: the claim purports to cover processes in which no problem is solved in an inventive manner, because there is no problem in the first place.

The Opposition Division (section 5.1 of the appealed decision) misunderstood the situation when they stated that "the opposition division is not in a position to decide if the proprietor's or the opponent's experiments show the correct and reproducible data". Notwithstanding our criticisms of the data in the patent (see section 4 above), D4 was not submitted in order to dispute the results reported in the patent. Rather, it was intended to show that an SD step does not necessarily raise ACA levels.

The OD was also wrong to fail to take into account (apparently) the evidence presented by D3, D8 and D13, similarly showing that an SD step does not necessarily raise ACA levels.

In view of the inadequacy of the data in the patent, the OD was further wrong to state that "the proprietor's experimental findings are based on a higher number of experiments" and to decide, on that basis, that there was problem that had been solved.

5.2 The patentee's criticisms of D4 indicate that the claim should be restricted

The patentee (sections 2.4 and 2.5 of the 19 May 2005 submission) criticised our **D4** evidence on the basis that (i) the D4 process used a CM Sepharose column (i.e. cation exchange chromatography) to remove the solvent and detergent (whereas the examples of the patent use diafiltration, and the general description (but not the specific Examples) refers to the use of hydrophobic chromatography) and (ii) the D4 experiments used two detergents (whereas the examples of the patent use just one). The implication seems to be that therefore one would not expect the initial steps of the D4 process to raise ACA.

Nevertheless, by using the term "comprising" and "a detergent", the claim purports to include a process that involves cation exchange chromatography to remove the SD reagents and an SD step that involves two detergents. The patentee has nicely underlined our point: the claim seems to cover processes in which the ACA is not raised to an unacceptable level at the end of step (b) and

therefore, if it does have such a scope, it covers processes in which the "invention" serves no technical purpose.

If the patentee regards such a process as being within the claim, then his previous criticism of D4 should be disregarded and D4 should be taken to be an example of a process in which the alleged problem simply does not arise, and thus the claimed process does not offer an inventive solution to anything.

5.3 The patentee's further criticisms of D4 are unjustified

The patentee has also (section 2.3 of the 19 May 2005 letter) suggested that the ACA level that was found with both of the preparations studied in the **D4** experiment is higher than that achieved in the patent and that therefore the patent offers an improvement. Our first point in response to this is to note that the ACA level, at 45.6, is actually lower than the level in the commercially-approved product of the D14 process, which had a level of 47.6 (see D15). Hence, a product having an ACA level of 45.6 is perfectly acceptable. Secondly, however, the declaration by Brian Crowe which we presented as D18 explains in some detail why it is impossible to compare the ACA levels that are reported in D4 and in D15 (both of which were assayed in accordance with the European Pharmacopoeia) with the ACA levels that are reported in the patent. As was explained by Dr Crowe, particularly in sections 10 to 13 of his declaration, the patent does not actually disclose the assay that was used. However, it can be seen that it was not the assay in the European Pharmacopoeia, which was the assay used in D4.

Hence, there is no evidence that the process described in the patent reduces the ACA to a level lower than that disclosed in D4.

5.4 The wording of the claim does not match the alleged problem/solution

The Board may wonder why the opponent should be concerned about a process that does not seem to solve a problem. The reason is that the wording of the claim does not correspond to the alleged problem and the alleged solution. More specifically, the claim does not state that step (a) of the process is carried out in such a way that the ACA level is raised to a level that is unacceptable for intravenous administration; and the claim does not state that step (c) of the process achieves a reduction of the ACA to a level that is acceptable for i.v. administration. In principle, therefore, the patent claim could be asserted against a competitor who carried out the SD process in such a way that the ACA was not raised to an unacceptable level (or who used other ways subsequently to reduce the ACA to an acceptable level, which owed nothing to the teaching of the patent) and then used a low pH incubation in order to reduce viral titre, as was taught in D23 and in D14. Those in the art should be free to carry out such processes without the threat of this inadequately supported and inadequately defined claim being asserted against them.

(Our comment that the claim is not restricted to a step (a) in which ACA is raised to an unacceptable level and nor is it restricted to a step (c) in which ACA is

reduced to an acceptable level should not be taken as an acknowledgement that a thus-amended claim would comply with the EPC.)

5.5 Possible reasons for the possibly raised ACA in the patent

As discussed in section 4.5 above, the data in the patent do not convincingly show that the ACA level was raised in the particular SD process that was used. Nevertheless, if one assumes for the sake of argument that it was raised, then it is interesting to try to determine why this should be, given that (as shown in section 5.1) an SD step does not necessarily raise the ACA level.

5.5.1 Residual SD reagents

In section 4.7 above, we showed that the patentee's experiment that was intended to show that the raised ACA could not be due to residual solvent and/or detergent in the preparation did not actually show this, since the 'control' experiment was badly designed. Specifically, the amount that was used in order to "spike" the antibody solution was not necessarily the amount that was left at the end of the SD removal step.

In fact, there are reasons for believing that the raised ACA level *was* caused by residual detergent. On page 5 lines 27 to 28, it is stated that the post-SD solutions were diafiltered with four volumes of water. However, in the inventor's post-published paper D25, page 13, middle of the first complete paragraph in the right-hand column, it is stated that:

> *"Cholate levels declined during the first three volumes of diafiltration; however, no decrease in cholate levels were* (sic) *detected after four volumes of diafiltration which suggests that a portion of the cholate was bound to protein."*

The opposed patent itself actually acknowledges that diafiltration may not be enough to get rid of the cholate. See page 4 of the patent at lines 32 to 34, where it is stated:

> *"In the present invention, hydrophobic chromatography is employed* ***to remove the TNBP and cholate not eliminated by the filtration and diafiltration steps;*** *and thus provide a final product with low levels of residual TNBP and cholate which is suitable for intravenous administration. Hydrophobic chromatography is a method for TNBP removal from protein solutions that has fewer drawbacks and limitations than other available methods such as oil extraction, ion exchange or affinity chromatography."* (emphasis added)

Why, then, was hydrophobic chromatography apparently not used in the preparation of the solutions on page 5 of the patent that were tested for ACA? It seems that the process was not carried out properly and hence the raised ACA was a self-inflicted problem that could have been overcome simply by taking more care to get rid of the SD reagents. Notice, for example, that the process of D10

employs first an oil extraction and then hydrophobic chromatography (on a C18 column) in order to get rid of the SD reagents; see column 3 lines 12-23. The D3 process employed an ion-exchange chromatography step to eliminate solvent and detergent; see page 338, 13 lines from the bottom of the left-hand column. The D7 process involved oil extraction and CM-Sepharose chromatography in order to achieve this result; see page S39, middle of right-hand column.

The discussion above has centred principally on cholate, which is one of the detergents used in the patent. However, similar considerations apply to the alternative detergent that was used, namely Tween 80. This was also the detergent that was used in the D11 process. In the right-hand column on page 84, D11 notes that, although the TNBP is easily removed,

> *"However, Tween 80 exists as detergent micelles and could bind to protein molecules by hydrophobic interactions . [11]. Successful removal of traces of Tween 80 (< 25 ppm) is accomplished by reprecipitation after solubilising the protein in a large volume of water. This volume was determined to be 40 vol equivalents of the protein precipitant (fig. 5). It can be observed from this figure that fewer volumes were not consistently effective in removing the residual Tween 80 from the protein solution."*

Therefore, once again, the diafiltration against only four volumes of water that was used in the principal experiment in the patent can be seen to be inadequate to remove the Tween 80.

Maybe the detergent micelles referred to in D11 would affect the ACA assay to provide the appearance of raised ACA.

In the ACA assay, the antibodies are first mixed with complement proteins and thus detergent present with the antibodies could inhibit complement protein function. Indeed, the ">100" numbers in Tables 1 and 7 seem to indicate a failure of the ACA assay. The result would be *low* lysis and therefore a recorded "high" ACA. It is known that cholate can affect protein activity, so it seems reasonable that cholate (and possibly Tween) could harm complement proteins.

Hence, in relation to both detergents (cholate and Tween), the process in the patent omits the sort of step that those in the art knew was necessary in order to remove the detergent.

5.5.2 Sub-optimal conditions for the SD step

In paragraph [0016] of the patent, it is stated that cholate should be used at a pH of 5.0-6.4, preferably 5.6, and that, at pH5.8, the viral inactivation only takes 1-2 hours, whereas at pH 7 a minimum of 10 hours is needed. However, as was reported in paragraph [0025], the actual pH that was used in the SD step in the experimental examples reported on page 5 of the patent was 7.0, and the step took 10 hours. It is possible that this unnecessarily prolonged step harmed the antibodies. We notice that, when pH5.8 was used (see heading in Table 7), 75%

of the 5% IGIV solutions and 67% of the 10% IGIV solutions had acceptable ACA levels. Indeed, the patentee notes at page 7 lines 30-31 that

> *"Generally, the non-incubated sterile bulk samples of material incubated at pH5.8 had lower ACA levels than the pH7.0 samples..."*

Hence, the experiments reported in Tables 1 and 3 should simply be disregarded as not reflecting the SD conditions that would be used by those skilled in the art.

5.5.3 Conclusion

This is a bad patent, based on bad statistics and bad process technology. It should not be allowed to stand, to the detriment of those who carry out the SD reagent removal step properly, as had been taught in the prior art, and thereby overcome any ACA problem that there may be, and who then use a low pH incubation as an additional antiviral step, as had also been taught in the prior art (for example in D23 and D14).

6. ADDITION OF SUBJECT MATTER

We maintain the objections that were advanced during the opposition phase, which are summarised in sections 6.3 to 6.6 of these grounds of appeal. However, we are also introducing two new objections, which are addressed in sections 6.1 and 6.2 below.

6.1 Possible omission of the function of step (c)

It is not entirely clear whether the function of step (c) of Claim 1 of the opposed patent is specified. The claim ends with the words *"to produce the antibody solution having low viral activity and low anticomplement activity"*, which is the overall objective of the process. Step (a) of the claim is explicitly stated to reduce viral titre. However, it is not clear whether step (c) is limited to one in which ACA is reduced. During the EPO opposition oral proceedings, when the opposition division indicated that the function of the step was not specified in the claim, the patentee did not disagree.

In the application as filed, Claim 1 indicated that the solution resulting from the SD treatment was incubated

> *"such that the anticomplement activity of the solution is reduced to an acceptable level suitable for intravenous administration".*

In the description, the incubation is first mentioned in the middle of page 3, where it is stated that:

> *"We have discovered that the incubation step is necessary to achieve an acceptable level of ACA low enough to allow the ISG to be administered by intravenous injection."*

Next, on page 9 (first complete paragraph), it is stated that the solution is incubated *"in order to provide a lowering of ACA levels"*. A few lines further on, it is stated that *"ACA levels are gradually lowered by incubation at pH 4.25 under low ionic strength conditions"*. The experiments that were then reported were intended to show that ACA is indeed reduced to an acceptable level in the incubation step, and this is reiterated in the "Conclusion" on page 17 of the application as filed.

Hence, if the patentee considers that the wording of step (c) of Claim 1 of the patent allows for the step to be conducted such that ACA is not reduced from an unacceptable level to an acceptable level, then the original disclosure of the application as filed has been extended, contrary to Article 123(2) EPC.

6.2 Omission of relationship of steps (a) and (c)

Our point about step (c) of Claim 1, set out in section 6.5 above, leads one to another conclusion under Article 123(2). In Claim 1 as filed, step (a) of the claim was said to lead to the antibody solution having "a given level of anticomplement activity" and, in step (c), "the anticomplement activity of the solution is reduced to an acceptable level suitable for intravenous administration". The clear implication of this is that the "given level" after step (a) is *not* acceptable and suitable for i.v. administration, because otherwise the level could not be *reduced* to an acceptable level.

The quotation from the middle of page 3 that we provided above, namely:

> *"We have discovered that the incubation step is **necessary** to achieve an acceptable level of ACA low enough to allow the ISG to be administered by intravenous injection."* (emphasis added)

also shows that, in the application as filed, the process was disclosed as being one in which the ACA was raised in the SD step to an unacceptable level.

In Claim 1 as granted, however, the references to "a given level of anticomplement activity" and to reducing it to an acceptable level have been omitted. The claim simply states that a low ACA product is produced by the end of the process.

The subject matter that was added by this deletion of an essential feature from Claim 1 as filed is therefore the disclosure of processes in which a low ACA product is produced without ACA being raised to an unacceptable level in step (a) and then reduced to an acceptable level in step (c).

6.3 Claim 1 should refer to the model system and to BVDV in particular

In the application as filed, there are only two disclosures of the $4\log_{10}$ feature. The first occurs at page 3, where it is stated that the viral inactivation step "in a model system" (our emphasis) preferably results in a $4\log_{10}$ reduction in the titre of lipid enveloped viruses. At the second location, namely the end of the first paragraph on page 7, the particular model system is disclosed in more detail, namely a combination of HIV-1 and BVDV. It is clear from this second location that, although the model system contained two viruses, it was specifically the inactivation of BVDV, and not the inactivation of HIV-1, that provides the basis for the $4\log_{10}$ feature.

In Claim 1 of the granted patent, on the other hand, there is a disclosure of a generalised process in which the titre of *any and all* lipid-enveloped viruses is reduced by at least $4\log_{10}$. One can easily imagine that the process conditions might need to be different in order to reduce by $4\log_{10}$ the titre of a lipid-enveloped virus that was not BVDV. No such process is disclosed in the application as filed.

Hence, the specific subject matter that was added, in contravention of Article 123(2) EPC, was the concept of a solvent-detergent process that would reduce the titre of any and all lipid-enveloped viruses by at least $4\log_{10}$, rather than just reducing the titre of the BVDV-based model system by at least $4\log_{10}$.

6.4 The "$4\log_{10}$" feature is technically significant

The patentee argued (19 May 2005, page 10) that the limitation in Claim 1 to the reduction of lipid enveloped viruses by at least $4\log_{10}$ does not provide a technical contribution to the subject matter of the invention but merely limits the protection of the claim.

This is inconsistent with the patentee's submissions in the first paragraph of section 2.6 of that letter. In the latter location, the patentee argued that D4 could not be taken as an indication that step (a) of the claim might not increase ACA, because the relevant step in the D4 experiments had not been shown to achieve a $4\log_{10}$ reduction of viral titre. In essence, therefore, in section 2.6 of the response, the patentee was saying that a solvent-detergent process that achieves a $4\log_{10}$ reduction of viral titre will increase ACA, whereas a solvent-detergent process that does not achieve a $4\log_{10}$ reduction of viral titre might not increase ACA. Since the whole point of the alleged invention is to reduce the ACA that is allegedly caused by the solvent-detergent process, it can be seen that, according to the patentee's own submissions, the $4\log_{10}$ reduction in viral titre undoubtedly provides a technical contribution to the subject matter of the claim.

6.5 The cross-reference to D1 is inadequate in this context

On page 11 of the 19 May 2005 letter, the patentee argued that the cross-reference to D1 at page 2, line 3, of the application as filed should be regarded as an adequate basis for the introduction of the $4\log_{10}$ feature in to claim 1, since D1 (at

column 4, lines 57 to 62) discloses that the process can be used to obtain a 4log inactivation of virus. For the following reasons, and in the light of the very strict EPO practice concerning Article 123(2) EPC and cross-references to documents (whether "incorporated by reference" or not), the cross-reference to D1 does not provide an adequate basis for this amendment to claim 1.

6.5.1 The cross-reference is not proper

According to Appeal Board decision T689/90, a cross-referenced document can provide a basis for a feature to be introduced into a claim only if the cross-reference satisfies the following four part test. Is it clear that

(a) protection is or may be sought for the feature?

(b) the feature contributes to solving the problem?

(c) the feature belongs to the invention/description?

(d) the feature is precisely defined and identifiable within the disclosure of the cross-referenced document?

The "feature" in question is the use of a solvent-detergent process that reduces by a factor of $4\log_{10}$ the titre of any and all lipid-enveloped viruses.

In answer to the first question of the four part test, it is by no means clear that protection was going to be sought for this feature. Indeed, at the end of the middle paragraph on page 3 of the application as filed, it was stated only that the reduction in viral titre was assessed by reference to a *model* system (which was specified later), not by reference to any and all lipid-enveloped viruses.

In answer to the second question, it is clear that the feature does *not* contribute to solving the problem. The solution to the problem that is set out in the application as filed is an incubation process in order to reduce ACA. Indeed, if the patentee's submissions in relation to inventive step are correct, then it is the solvent-detergent step that *creates* the problem; it certainly does not solve it.

In relation to the third question, it should be noted that the cross-reference to the D1 document is in the part of the opposed specification that is headed "Background of the Invention". There is no cross-reference to D1 in the "Summary of the Invention" or the subsequent description of specific embodiments in the present application as filed.

The fourth question in the test is generally taken to mean that, when the reader of the European application looks at the cross-referenced document, he is clearly led to the feature in question. For example, the European application might state that "Any of the adhesives disclosed in document X can be used" and then he knows that he should look at the parts of X that disclose adhesives. It is clear that the cross-reference to D1 on page 2 of the application as filed does *not* lead the reader to the paragraph towards the end of column 4 of D1, in which a specific reduction of viral titre is disclosed.

According to Decision T689/90, a cross-reference must pass *all four* of these tests in order for the cross-referenced subject matter to be introduced into the European specification without contravention of Article 123(2). As we have shown above, the cross reference on which the patentee relies does not pass *any* of these tests. Hence, the introduction of the feature contravened Article 123(2) EPC.

6.5.2 D1 does not disclose the feature anyway

As noted above, the offending feature in claim 1 is the disclosure of a solvent-detergent process that reduces by at least $4\log_{10}$ the titre of *any and all* lipid-enveloped viruses. Even if the cross-reference to D1 were proper (which, for the reasons explained above, is not the case), the feature still cannot be found in D1. The relevant disclosure in D1 is at column 4, lines 57 to 62. This refers to "inactivation of virus" and it is clear from the preceding passages that the viruses in question are simply the various *hepatitis* viruses, not any and all lipid-enveloped viruses.

Hence, whether one refers to the legal standard established on T689/90 or to the technical content of D1, it is evident that the cross-reference to D1 does not help the patentee.

We therefore maintain the arguments under Art 100(c) EPC that were submitted in the opposition phase.

6.6 The OD erred in its finding under Article 123(2) EPC

On page 4 of the appealed decision, the opposition division stated that the $4\log_{10}$ feature was disclosed in the application as filed, at the end of the second paragraph on page 3. However, the OD seemingly did not take into account the fact that the disclosure at that point is solely in relation to a model system, using particular viruses.

The OD also stated that "it is further clear from the cited prior art (cf. i.a. D1) that the reduction of 4log10 is generally accepted as an appropriate numerical value". This statement is legally unsupportable. The disclosure of the 4log10 feature in D1 cannot be regarded as amounting to common general knowledge, nor that the value is "generally accepted" as being appropriate in relation to all viruses. As noted above, the disclosure in D1 itself was specific to a particular virus.

Finally, the OD characterised the amendment to claim 1 has been one that "merely clarifies the original expression 'substantial reduction' and thus the scope of protection sought". However, a clarification of a claim has to be made on the basis of the original disclosure, otherwise it does not comply with Article 123(2) EPC. The particular "clarification" at issue here was not based on the application as filed, because it was generalised to all viruses.

The opposition division therefore reached an erroneous conclusion in this regard.

7. CONCLUSIONS

The patent does not comply with Article 56 EPC.

The amendments to claim 1 in relation to the $4\log_{10}$ reduction of viral titre and to delete the respective references to ACA level in steps (a) and (c) contravened Article 123(2) EPC.

The Opposition Division's decision should therefore be set aside and the patent should be revoked.

8. ADDITIONAL DOCUMENTS CITED

D25 Alonso *et al* (2000) *Biologicals* 28, 5-15

D26 Gao *et al* (1993) *Vox Sang.* 64, 204-209

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